Remarks/Arguments:

Claims 27-49, presented hereby, are pending.

Claims 1-26 are canceled hereby, without prejudice or disclaimer.

Present claims 27-49 contain the subject matter of claims 1-21, revised in order to address issues raised in the Office Action (explained below) and to, otherwise, more clearly define the instant invention.

Claims 22-26 are cancelled pursuant to the restriction requirement. Applicants reserve the right to prosecute the non-elected subject matter of the cancelled claims in a divisional application.

Claim 3 was rejected under 35 USC 101 for allegedly not "setting forth any steps involved in the [claimed] process" (Office Action, page 2). Reconsideration of the rejection is requested.

In accordance with the instant amendment, claim 3 is amended, as present claim 29, to be dependent on present claim 36 (corresponding to original claim 9). Present claim 36 includes a "treatment" step and, so, the step of "evaluating" a treatment for Alzheimer's disease (recited in present claim 29) is, in fact, a step involved in the claimed process. Therefore, withdrawal of the rejection appears to be in order.

Claims 1-21 were rejected under 35 USC 112, first paragraph, for allegedly lacking enablement. Reconsideration is requested.

According to the statement of rejection, the instant specification is enabling for prognosing/predicting whether a subject suspected of having Alzheimer's disease clinically is at increased risk of developing Alzheimer's disease. The statement of rejection, however, regards the

presently claimed invention subject to the diagnosis of Alzheimer's disease as being not enabled. The statement of rejection refers to methods using unknown antibody preparations that are not further compared to specifically defined age-matched control values.

Applicants draw attention to the provided guidance and working examples in the present specification for the use of defined antibodies for nerve growth factor (NGF) (Examples 1 and 2 on pages 13, 14, and 15) and for neurotrophin 3 (NT-3) (Example 3 on page 16). The antibodies used are well defined antibodies, namely monoclonal anti-beta (2.5S, 7S) NGF antibodies (clone 27/21 from Boehringer Mannehim) and those antibodies for NT-3 that are part of the ELISA system (commercially available from Promega, Madison, WI), as well as anti-human-NT-3 polyclonal antibodies.

Further, performing an ELISA immunoassay was well-known in the art. The instant specification (pages 13, 14, and 16) clearly describes the ELISA assay and its standardization as used in accordance with the presently claimed invention. Additionally, applicants refer to the method as described in Weskamp et al. (J. Neurochem. 1987, 48: 1779-1786). "In satisfying the enablement requirement, an application need not teach, and preferably omits, that which is well known in the art." *Staehelin v. Secher*, 24 USPQ2d 1513, 1516 (BPA & I 1992).

The statement of rejection rightfully states that the detection levels of NGF and/or NT-3 in the CSF from Alzheimer's patients are all different in the publications of Massaro et al., 1994 (Ref#: M), Murase et al., 1993 (Ref#: L), Nishio et al., 1998 (Ref#:1), Gilmore et al., 1997. This is due to the fact that different antibodies, different ELISA systems, and different standards for the

standardization procedure are used in the referenced publications. For example, Massaro et al. used anti-mouse NGF monoclonal and polyclonal antibodies and another detection system (alphaD11 conjugated to horseradish peroxidase) and achieved a detection limit of 28pg betaNGF/ml; whereas, Murase et al. used an anti-human NGF antiserum in a two-site enzyme immunoassay with a beta-D-galactosidase detection system and indicated a sensitivity of 03. pg/ml NGF. Nishio et al. describes the use of polyclonal rabbit anti-murine beta-NGF antibodies, the use of another standard, and a detection limit of 1 pg/ml NGF. Thus, it is not unexpected that completely different sensitivities, i.e., detection limits, and hence different values are obtained. A person skilled in the art, provided that he is using the same ELISA system, the same standardization, the same antibodies, and the guidance provided in the present application, will be enabled to make and use the invention as presently claimed without undue experimentation and with the same parameters as set forth therein.

Furthermore, applicants point to appropriate reference values, to specifically defined control values (healthy control subjects not suffering from Alzheimer's disease, CTR) for NGF/NT-3 (application Figures 1 and 2), which are obtained by following the teachings provided in the subject application.

The statement of rejection observes that Scinto et al., 1994, teach that a definitive diagnosis of Alzheimer's disease is only possible by histological examination of brain tissue. Applicants submit that this notion, indeed, would underscore the urgent need for diagnostic testing as given in accordance with the instant invention as claimed. To applicants' knowledge, no diagnostic test in any medical field has ever reached a 100% confirmation level. Each method of testing has a certain

threshold value below which detection of disease is not possible. Even diagnostic tests carried out by, for instance, laboratory techniques, ultrasound, radiography, computer tomography (CT), and others, are inherently imperfect. The result of any diagnostic test should be viewed as a given likelihood to have, or to develop a certain disease. Thus, applicants point to the fact that the method of diagnosing as presently disclosed and claimed has extremely high utility when a confirmation level of 90.1% is reached. The accuracy of the diagnosis of Alzheimer's disease by determining the level of NGF and/or NT3 has been verified in that postmortem brain tissues of all persons suspected of having had said disease have been examined histologically. Therefore, applicants submit that the invention of a diagnostic method for Alzheimer's disease as presently disclosed and claimed is working very well and is very valuable.

Claims 1-21 were rejected under 35 USC 112, ¶2, for allegedly being indefinite. Reconsideration is requested.

A "reference value" indicates a range or distribution of a measurement of a certain parameter value in a population that has been selected for either the presence or the absence of the disease in question. Thus, a "reference value" represents a "level" and/or an "activity" of NGF and/or of NT3, which is representative and indicative for a known health or disease status and to which an individual "level" and/or "activity" of NGF and/or NT3 in a sample from a subject can be compared. Applicants refer to the wording "healthy control subject" (CTR), which, in the present by claimed invention, is used tantamount to the term "reference" and is defined on pages 12 and 13 of the instant application as filed. It is commonly known in the art that the value obtained from analyzing a

"reference" is the "reference value". Reference values obtained from the references in accordance with the presently claimed invention are shown, for example, in application Figures 2 and 3. Further, the control subjects are not putative control subjects; on the contrary, the control subjects are very well defined by the examination procedure described in the instant application and, thus, they are not considered to be at increased risk of developing Alzheimer's disease.

The statement of rejection relies on an alleged failure to define a "reference sequence" in connection with claims 4, 13 and 19. Since the term "reference sequence"does not appear in the rejected claims, it appears to be irrelevant under §112, ¶2. When the claims "do not require" the subject matter at issue, enablement with respect to such subject matter is not required under § 112, paragraph one. *Ex parte Erlich*, 3 USPQ 2d 1011, 1014 (BPA&I 1987).

Concerning claim 6, it has been shown that several animal models known in the art (mouse, rat, dog) are developing pathological hallmarks, which are very similar to those observed in human patients with Alzheimer's disease. Additionally, there are animals known to naturally develop Alzheimer's disease-like symptoms, for example, the primate limurian *Microcebus murinus* (Giannakopoulos et al., Acta Neurophathol. 1997, 94: 131-139). Thus, it appears that Alzheimer's disease is not unique to humans.

Claims 5 and 16 are rejected under 35 USC 112, ¶2, for allegedly being indefinite. Reconsideration is requested.

Both ranges of limitations, the broad range of 4 pg/ml to 25 pg/ml and the narrow range of 4 pg/ml to 14 pg/ml, are features of the claims. By the instant amendment the subject matter of

claim 5 is divided into two dependent claims, i.e., claims 31 (reciting the broad range limitation 4 pg/ml to 25 pg/ml) and claim 32 (reciting the narrow range limitation 4 pg/ml to 14 pg/ml). Similarly, the subject matter of claim 16 is divided into present claims 43 and 44.

Claims 9, 10, and 21 are rejected under 35 USC 112, ¶2, for allegedly being indefinite, i.e., there being no antecedent basis for the recitation "said sample gatherings" (claim 9) and "said treatment" (claim 10) and, further, as no specific disease state to be "treated" is recited (claim 21). Reconsideration is requested in view of the changes to the claims effected, hereby.

Present claim 36 (amended claim 9) recites the method "wherein said subject receives ...", and claim 37 (amended claim 10) recites the method "wherein said level and/or activity in said samples ...". Present claim 49 (amended claim 21) limits the recited "therapeutic treatment" to a treatment "for Alzheimer's disease." Accordingly, the rejection appears to be overcome and, so, withdrawal of the rejection is in order.

Reconsideration is requested with respect to the rejection of claims 14-21 (particularly claims 14 and 17) under 35 USC 112, ¶2 in that the word "selectively" does not appear in the present claims. That is, by the instant amendment "selectively detects" is replaced by "detects."

Reconsideration is requested with respect to the rejection of claims 3, 20, and 21 under 35 USC 112, ¶2, for allegedly being indefinite.

According to the statement of rejection, the rejected claims are allegedly indefinite as they recite "the method according to claim 1 ..." and "for use in monitoring ...", but allegedly do not set forth any active steps involved in the method/process and, further, for allegedly not reciting "

positive steps deliminating *how* this use is actually practiced (Office Action page 8, *emphasis added*).

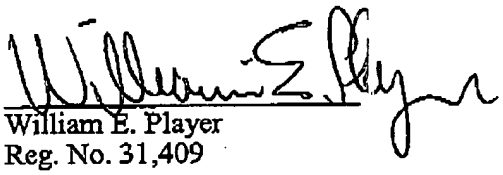
Applicants submit that the rejected claims do, in fact, set forth active steps involved in the claimed process, namely, determining a level ..., which in itself comprises many active steps, for instance, measurements by ELISA systems ..., and comparing said level ... Thus, active steps in the rejected claims clearly indicate a process as the instant invention (cf. Examples 1 to 3, pages 11 to 17, of the instant application).

As for not reciting "*how*" the claimed invention ("use") is "practiced," the statement of rejection confuses the function of the claims, on the one hand, with the function of the specification, on the other; i.e., the claims define the legal limits of the invention, the specification details *how* the invention is to be *practiced*. *In re Roberts*, 176 USPQ 313, 315 (CCPA 1973).

Favorable action is requested.

Respectfully submitted,

JACOBSON HOLMAN PLLC

By 
William E. Player
Reg. No. 31,409

400 Seventh Street, NW
The Jenifer Building
Washington, D.C. 20004
Tel. (202) 638-6666
Fax (202) 393-5350
Date: December 29, 2003
WEP/bap
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